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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/949,904	10/15/1997	EDWARD R. LAVALLIE	GI-5288B	8744

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ART UNIT	PAPER NUMBER
1642	28

DATE MAILED: 03/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/949,904	Lavallie et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 16, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *18-20, 22, 23, 25, and 29* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *18-20, 22, 23, 25, and 29* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

1. Upon review and reconsideration, the finality of the previous office action is withdrawn.

2. The Amendment filed July 26, 2001 (Paper No. 23) in response to the Advisory Action of August 8, 2000 and the telephone conferences of May 8, 2001 and June 14, 2001 is acknowledged and has been entered in part. It is noted that the amendment filed October 28, 1999 (Paper No. 14) was not entered, therefore the amendments recited in that amendment were not entered. Although Applicant cancels claims 30-32 (added in Paper No. 20) the cancellation is moot since the claims were never entered. Further, Applicant amends claim 20, based on the amendment of claim 20 in Paper No. 14 which was also not entered. Since the amendment is improper, the amendment of claim 20 will not be entered. Further, the Amendment filed March 14, 2002 (Paper No. 26, in response to the telephone messages of March 4 and 5) is acknowledged and has been entered. Applicant properly amends claim 20 as recited in Paper No. 9. Claim 28 has been canceled, claims 18 and 20 have been amended and Claims 18-20, 22,23, 35 and 29 are currently under prosecution.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

5. Claim 20 remains rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 12, Section 4, pages 2-4.

Applicant argues that claim 20 has been amended to depend from claim 18 and to include the phrase "in a pharmaceutical carrier". The argument has been

considered but has not been found persuasive because the claim as amended in Paper No. 26 does not recite the phrase "in a pharmaceutical composition". Further, the claim is still drawn to a composition for the formation and/or maintenance of chondrocyte and/or cartilagineous tissue in a patient in need of the same which still reads on a "pharmaceutical composition". Further, although now drawn to chrondrocyte and or cartilagineous tissue, for the reasons previously set forth, the specification is not enabling for the *in vivo* treatment of any disease or condition.

Claim Rejections - Double Patenting

6. Claims 18-20, 22, 23, 25 remain rejected and Claim 29 is rejected under the judicially created doctrine of double patenting for the reasons previously set forth in paper No. 12, Section 5, pages 4-5.

Applicant argues that in a discussion with Examiner, it was determined that a terminal disclaimer is not necessary for claims 19, 22, 23, 25 because USSN 08/848,439 is still pending. The argument has been considered but has not been found persuasive because Applicant was told that when a case is allowed and a pending sibling case is still pending, a terminal disclaimer is not required in the allowed case. However, it is noted that the instant application is not allowable at this time. However, rejection will be held in abeyance until such time as either USSN 08/848,439 or the instant application is found allowable.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

7. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement

thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

8. Claims 1-8 are rejected under 35 USC 101 because the claimed invention is not supported by a substantial utility, a well established utility or a credible utility.

The specification speculates that the disclosed utilities for the human SDF-5 protein and truncated versions of that protein may include the ability to regulate the binding of Wnt proteins to protein receptors and may further include the ability to regulate the formation, differentiation, proliferation and/or maintenance of cells and/or tissues, for example connective tissues and may include the ability to enhance and/or inhibit the formation, growth, proliferation, differentiation and/or maintenance of chondrocytes and/or cartilage tissue (p. 5, lines 7-17). The specification speculates that human SDF-5 protein pharmaceutical compositions may be used in formation of chondrocytes and/or cartilage tissue phenotype, may be utilized in order to enhance and/or inhibit the formation, growth proliferation, differentiation and/or maintenance of beta cells and other cell types as well as organs such as liver, spleen, brain, lung, cardiac and kidney tissue and that a composition comprising human SDF-5 protein may be used to treat precursor or stem cells in order to enhance the formation, differentiation, proliferation and/or maintenance of such cells, tissues and organs. The specification further speculates that human SDF-5 protein containing compositions may be employed in methods for treating a number of tissue defects, healing and maintenance of various types of tissues and wounds and that the tissues which may be treated include cartilage, epidermis, nerve, muscle, , connective tissue, bone, tendon, ligament and other tissues . The human SDF-5 containing compositions may be used to treat or

prevent rheumatoid arthritis, osteoarthritis, and other abnormalities of cartilaginous or other organs and tissues (para bridging pages 7-8). Additionally the specification speculates that the proteins may be useful for induction of growth and/or differentiation of embryonic cells and/or stem cells and thus may be useful for treating cell populations (p. 10, lines 32-35). SDF-5 may be useful for treating cell populations to enhance and/or inhibit the formation, differentiation, proliferation and/or maintenance of chondrocytes, cartilaginous tissue (p. 11, lines 5-10). Further, the SDF-5 gene appears to encode a secreted factor, thus providing soluble receptors which may be capable of binding with the Wnt proteins, initiating and/or blocking signal transduction. The potential signal transduction regulation activities of these proteins suggests that human SDF-5 is an important regulator of differentiation of tissues and organs and may be involved in the induction, formation, growth, differentiation proliferation and/or maintenance of tissues and organs (p. 11, lines 12-24). In particular, it has been observed by the inventors that the human SDF-5 protein may be useful for the induction, formation, growth, differentiation, proliferation and/or chondrocytes, cartilaginous tissue (p. 11, lines 5-10). Further, SDF-5 gene appears to encode a secreted factor, thus providing soluble receptors which may be capable of binding with the Wnt proteins, thus initiating and/or blocking signal transduction. The potential signal transduction regulation activities of these proteins suggests that human SDF-5 is an important regulator of differentiation of tissues and organs and may be involved in the induction, formation, growth, differentiation proliferation and/or maintenance of tissues and organs (p. 11, lines 12-24). Thus these proteins may be useful in the treatment of cartilage disorders, such as osteoarthritis, rheumatoid arthritis and

articular cartilage defects and in the enhancement and/or inhibition of cellular formation, growth, differentiation, proliferation and/or maintenance, formation of chondrocytes and/or cartilage tissue (p. 11, lines 24-31). The specification continues to speculate as to other possible useful properties for SDF-5 these properties being characteristic of the broadly different Frazzled family of proteins and include angiogenic, chemotactic and/or chemoattractant properties, induction or formation of cells capable of secreting valuable hormones such as insulin, glucagon or other endocrine or exocrine hormones (p. 20, lines 11-19). The proteins of the present invention are expected to exhibit one or more of the following uses including determination of biological activity, including one of a panel of multiple proteins for high throughput screening, raising antibodies, quantitatively determining the levels of protein in biological fluids, markers for tissues in which the corresponding protein is preferentially expressed, identification of proteins to which the protein binds (p. 23, lines 18-30) and the protein may also be used as a nutritional source (p. 24, line 10). The specification goes on to speculate that the protein may exhibit cytokine and cell proliferation/differentiation activity (p. 24, line 18), immune stimulating or suppressing activity (p.26, line 11), hematopoiesis regulating activity (p. 32, line 14), tissue growth activity, page 33, line 34), activin/inhibin activity (p. 36, line 24), chemotactic/chemokinetic activity (p. 37, line 14), hemostatic and thrombolytic activity (p. 38, line 14), receptor/ligand activity (p. 38, line 29), anti-inflammatory activity (p. 39, line 21), tumor inhibitory activity (p. 40, line 4) and assays for determining whether or not the SDF-5 protein has any of these activities (see pages 24-40). and assays for determining whether or not the protein of the invention has these activities. Finally, the specification

speculates on the possibility that the protein of the invention may also exhibit any one of a laundry list of physiological activities (para bridging pages 40-41).

However, neither the specification nor any art of record teaches what the claimed polypeptides are, what they do, they do not teach a substantial, credible or well established utility for any of the claimed polypeptide products do not teach a specific, substantial, credible or well established relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The asserted utility of the claimed polypeptides is based on the assertion that the SDF-5 polypeptide has homology to the Wnt binding domain of frizzled/frazzled family of proteins (p. 4, lines 5-15) and that the human SDF-5 gene has homology to murine SDF-5. However, it was well known in the art, at the time the invention was made, that there was not a single Wnt family protein. Finch et al (PNAS, 1997, 94:6770-6775, IDS item) specifically teach that the Wnt family of proteins consists of more than a dozen structurally related molecules and that the Wnt family of proteins are involved, as extracellular signaling molecules, in cellular proliferation, migration, differentiation and tissue morphogenesis. Specifically Wnt proteins have been demonstrated to have important roles in development of midbrain and cerebellum, kidney tubologenesis and limb bud development (p. 6770, col 1). Further, Wang et al (JBC, 1996, 271:4468-4476, IDS item) specifically teaches that the Frizzled family is a large family of putative transmembrane receptors, 19 of which have been identified. These receptors are likely to play multiple roles in vertebrate development and/or physiology. Further the expression of frizzled family members in many different tissues and during embryonic development suggests that they are involved in a wide variety of developmental and/or homeostatic processes.

Although the specification speculates that the encoded protein of SEQ ID NO:2/3 may be capable of binding the Wnt protein and thus capable of regulating the binding interaction of Wnt gene products to receptor proteins, there is no teaching of which of the more than a dozen Wnt proteins SEQ ID NO:2/3 would be capable of binding or which receptor binding interactions SDF-5 would be capable of regulating. Further, although the specification states that SDF-5 has a sequence with homology to the Wnt binding domain, the specification does not teach how much homology there is to that domain, does not teach what the consensus sequence of the Wnt binding domain is (it is noted that although a search of the literature revealed that the Wnt binding domain is a cysteine rich domain with a partial sequence of CRD, a review of SEQ ID NO:2 did not reveal either this partial consensus sequence or a cysteine rich domain). In view of the lack of information on the consensus sequence, and the apparent lack of consensus sequence in the SDF-5 protein, one would not believe that it is more likely than not that the claimed protein is a Wnt binding protein. Further, even if there were some homology to a Wnt binding domain, the effects of dissimilarities between the consensus domain and the putative binding domain of the claimed polypeptide on the binding functions of the claimed proteins cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is

extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Given the sensitivity to specific binding required by a receptor, it is not credible and no one of skill in the art would believe it more likely than not that the claimed protein is a Wnt binding protein or accept the assertion that the claimed protein is a Wnt binding protein in the absence of a consensus sequence for Wnt binding. In order to determine how to use the claimed polypeptide, additional experimentation must be done. Therefore the claimed polypeptide does not have substantial utility. The suggested homology to Wnt binding proteins does not provide a well established

utility because even were the claimed polypeptide a Wnt binding protein, given the known heterogeneity of Wnt binding proteins and their broadly diversified functions, it is not possible to determine from the information in the specification which, or whether, the claimed polypeptide demonstrates any of the functions of the diverse group and thus the homology does not provide a well-established utility.

As drawn to the homology of human SDF-5 to murine SDF-5, Finch et al, *Supra*, specifically teach that at the time the invention was made, little was known about the activity of murine SDF-5 (p. 6774, col 2). In addition, Shirozu et al (Genomics, 1996, 37:273-280) teach that although murine SDF-5 shows some homology to the extracellular domains of a frizzled gene, its C-terminus has no homology with frizzed. Further Shirozu et al teach that SDF-5 mRNA was expressed in brain, heart, kidney, lung and thymus but not in liver and spleen. A review of the specification revealed that the putative human homologue of murine SDF-5, although expressed in mammary gland was not expressed in brain, lung, heart kidney. It is clear that the expression pattern of the mouse and human homologues are different. Importantly, Bork (Genome Research, 2000,10:398-400) clearly teaches that protein function is context dependent and that in determining protein function, both molecular and cellular aspects have to be considered (p. 398, col 2). Thus, even if human SDF-5 is an SDF-5-like protein or a Wnt binding protein, neither the specification nor any art of record teaches what the polypeptide is, what it does, does not teach a credible relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease. Neither the limited homology to Wnt binding proteins nor the homology to murine SDF-5 supports a well-established utility for the reasons set forth above. Further,

the laundry list of hypothesized, possible utilities cited does not provide support for a well-established utility for the reasons set forth above. Given the unknown function of murine SDF-5 and the apparent lack of a consensus sequence for Wnt binding protein, the hypothesized utilities do not appear to be support a credible utility. Further, additional research is required on the polypeptide itself in order to determine how to use the claimed polypeptides, thus the claimed invention does not have substantial utility. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptides.

Claim Rejections - 35 USC § 112

9. Claims 18-20, 22, 23, 25 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The claims are drawn to human SDF-5 protein and truncated versions of that protein. The specification teaches that the SEQ ID NO:2/3 are "frazzled" proteins . Further the specification teaches that "frazzled" activity includes the ability to bind to Wnt proteins and thus SEQ ID NO:2/3 may have the ability to regulate the binding of Wnt proteins to protein receptors and may further include the ability to regulate the formation, differentiation, proliferation and/or maintenance of cells and/or tissues, for example connective tissues and may include the ability to enhance and/or inhibit the formation, growth, proliferation, differentiation and/or maintenance of chondrocytes and/or cartilage tissue (p. 5, lines 7-17). The specification teaches that human SDF-5 protein pharmaceutical compositions may

be used in formation of chondrocytes and/or cartilage tissue phenotype, may be utilized in order to enhance and/or inhibit the formation, growth proliferation, differentiation and/or maintenance of beta cells and other cell types as well as organs such as liver, spleen, brain, lung, cardiac and kidney tissue and that a composition comprising human SDF-5 protein may be used to treat precursor or stem cells in order to enhance the formation, differentiation, proliferation and /or maintenance of such cells, tissues and organs. The specification further teaches that human SDF-5 protein containing compositions may be employed in methods for treating a number of tissue defects, healing and maintenance of various types of tissues and wounds and that the tissues which may be treated include cartilage, epidermis, nerve, muscle, , connective tissue, bone, tendon, ligament and other tissues . The human SDF-5 containing compositions may be used to treat or prevent rheumatoid arthritis, osteoarthritis, and other abnormalities of cartilaginous or other organs and tissues (para bridging pages 7-8). Additionally the specification teaches that the proteins may be useful for induction of growth and/or differentiation of embryonic cells and/or stem cells and thus may be useful for treating cell populations (p. 10, lines 32-35). SDF-5 may be useful for treating cell populations to enhance and/or inhibit the formation, differentiation, proliferation and/or maintenance of chondrocytes, cartilaginous tissue (p. 11, lines 5-10). Further, the SDF-5 gene appears to encode a secreted factor, thus providing soluble receptors which may be capable of binding with the Wnt proteins, initiating and/or blocking signal transduction. The potential signal transduction regulation activities of these proteins suggests that human SDF-5 is an important regulator of differentiation of tissues and organs and may be involved int eh induction,

formation, growth, differentiation proliferation and/or maintenance of tissues and organs (p. 11, lines 12-24). In particular, it has been observed by the inventors that the human SDF-5 protein may be useful for the induction, formation, growth, differentiation, proliferation and/or maintenance and repair of chondrocytes and or/cartilage tissue. Thus these proteins may be useful in the treatment of cartilage disorders, such as osteoarthritis, rheumatoid arthritis and articular cartilage defects and in the enhancement and/or inhibition of cellular formation, growth, differentiation, proliferation and/or maintenance, formation of chondrocytes and/or cartilage tissue (p. 11, lines 24-31). The specification continues to speculate as to other possible useful properties for SDF-5 those properties being characteristic of the Frazzled family of proteins and include angiogenic, chemotactic and/or chemoattractant properties, induction or formation of cells capable of secreting valuable hormones such as insulin, glucagon or other endocrine or exocrine hormones (p. 20, lines 11-19). The proteins of the present invention are expected to exhibit one or more of the following uses including determination of biological activity, including as one of a panel of multiple proteins for high throughput screening, raising antibodies, quantitative determination of the levels of protein in biological fluids, markers for tissues in which the corresponding protein is preferentially expressed, identification of proteins to which the protein binds (p. 23, lines 18-30) and the protein may also be used as a nutritional source (p. 24, line 10). The specification goes on to speculate that the protein may exhibit cytokine and cell proliferation/differentiation activity (p. 24, line 18), immune stimulating or suppressing activity (p.26, line 11), hematopoiesis regulating activity (p. 32, line 14), tissue growth activity, page 33, line 34), activin/inhibin activity (p. 36, line 24),

chemotactic/chemokinetic activity (p. 37, line 14), hemostatic and thrombolytic activity (p. 38, line 14), receptor/ligand activity (p. 38, line 29), anti-inflammatory activity (p. 39, line 21), tumor inhibitory activity (p. 40, line 4) and assays for determining whether or not the SDF-5 protein has any of these activities (see pages 24-40). and assays for determining whether or not the protein of the invention has these activities. Finally, the specification speculates on the possibility that the protein of the invention may also exhibit any one of a laundry list of physiological activities (para bridging pages 40-41).

One cannot extrapolate the teachings of the specification to the enablement of the claims because it is not possible to determine from the specification how to use the protein because it cannot be determined which or how many, or even if any of the multitude of speculated, potential possible uses of the protein are actually uses to which the claimed protein can be put or whether any of the speculated, potential, possible properties of the claimed protein are actually properties that the claimed protein possesses. For example, although the specification teaches that the protein has homology to the Wnt binding domain of the frizzled/frazzled family of proteins, (p. 4, lines 5-15) and the specification teaches that it is of particular interest that the human SDF-5 gene appears to encode a secreted factor which may be capable of binding the Wnt protein and thus may be capable of regulating the binding interaction of Wnt genes to receptor proteins (para bridging pages 10-11), it was well known in the art, at the time the invention was made, that there was not a single Wnt family protein. Finch et al (PNAS, 1997, 94:6770-6775, IDS item) specifically teach that the Wnt family of proteins consists of more than a dozen structurally related molecules and that the Wnt family of proteins are involved, as

extracellular signaling molecules, in cellular proliferation, migration, differentiation and tissue morphogenesis. Specifically Wnt proteins have been demonstrated to have important roles in development of midbrain and cerebellum, kidney tubologenesis and limb bud development (p. 6770, col 1). Further, Wang et al (JBC, 1996, 271:4468-4476, IDS item) specifically teaches that the Frizzled family is a large family of putative transmembrane receptors, 19 of which have been identified. These receptors are likely to play multiple roles in vertebrate development and/or physiology. Further the expression of frizzled family members in many different tissues and during embryonic development suggests that they are involved in a wide variety of developmental and/or homeostatic processes. Although the specification speculates that SEQ ID NO:2/3 may be capable of binding the Wnt protein and thus capable of regulating the binding interaction of Wnt gene products to receptor proteins, there is no teaching of which of the more than a dozen Wnt proteins SEQ ID NO:2/3 would be capable of binding or which receptor binding interactions SDF-5 would be capable of regulating. Further, although the specification states that SDF-5 has a sequence with homology to the Wnt binding domain, the specification does not teach how much homology there is to that domain, does not teach what the consensus sequence of the Wnt binding domain is (it is noted that although a search of the literature revealed that the Wnt binding domain is a cysteine rich domain with a partial sequence of CRD, a review of SEQ ID NO:2 did not reveal either this partial consensus sequence or a cysteine rich domain). In view of the lack of information on the consensus sequence, and the apparent lack of consensus sequence in the SDF-5 protein, one could not predict, nor would one expect that the claimed protein is a Wnt binding protein. Further, even if there were

some homology to a Wnt binding domain, the effects of dissimilarities between the consensus domain and the putative binding domain of the claimed polypeptide on the binding functions of the claimed proteins cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These

references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Given the sensitivity to specific binding required by a receptor, no one of skill would accept the assertion that the claimed protein is a Wnt binding protein in the absence of a consensus sequence for Wnt binding.

Further, the specification appears to base the putative uses for human SDF-5 on the murine SDF-5, however, Finch et al, *Supra*, specifically teach that at the time the invention was made, little was known about the activity of murine SDF-5 (p. 6774, col 2). In addition, Shirozu et al (Genomics, 1996, 37:273-280) teach that although murine SDF-5 shows some homology to the extracellular domains of a frizzled gene, its C-terminus has no homology with frizzed. Further Shirozu et al teach that SDF-5 mRNA was expressed in brain, heart, kidney, lung and thymus but not in liver and spleen. A review of the specification revealed that the putative human homologue of murine SDF-5, although expressed in mammary gland was not expressed in brain, lung, heart kidney. It is clear that the expression pattern of the mouse and human homologues are different. Importantly, Bork (Genome Research, 2000,10:398-400) clearly teaches that protein function is context dependent and that in determining protein function, both molecular and cellular aspects have to be considered (p. 398, col 2). Thus, even if human SDF-5 is an SDF-5-like protein or a Frizzled/Frazzled related protein, given the information in the specification and the art, it cannot be predicted how to use SEQ ID NO: 2/3 based on its sequence similarity to the murine SDF-5 or its localization pattern. In view of the above, given the speculative nature of the specification and what is

known in the art, one of skill in he art would be forced into undue experimentation to practice the claimed invention

10. . If Applicant were able to overcome the rejections under 35 USC 101 and 35 USC 112 first paragraph above, Claim 25 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a human SDF-5 protein having a molecular weight of about 30 to 35 kd comprising the amino acid sequence of SEQ ID NO:3, does not reasonably provide enablement for a human SDF-5 protein having a molecular weight of about 30 to 35 kd comprising the amino acid sequence of SEQ ID NO:3 and having the ability to regulate the transcription of one or more genes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim.

The claim is drawn to a human SDF-5 protein having a molecular weight of about 30 to 35 kd comprising the amino acid sequence of SEQ ID NO:3 having the ability to regulate the transcription of one or more genes. The specification teaches that the SDF-5 gene **appears** to encode a secreted factor, thus providing soluble receptors and speculates that the protein encoded by the gene **may** be capable of binding with the Wnt protein, thus initiating and/or blocking signal transduction. The **potential** signal transduction regulatory activity of this protein suggests that SDF-5 **may** be an important cell regulator (emphases added) (p. 11, lines 12-24). The specification goes on to speculate that, because of a suggested homology to "frazzled" proteins (p. 5, lines 7-17), SDF-5 protein can have any one or a combination of a whole laundry list of properties (see pages 11-40) some of which appear to be associated with some frazzled proteins and some of which do not

appear to be associated with any frazzled proteins. One cannot extrapolate the teaching of the specification to the scope of the claims because other than the suggestion that SDF-5 appears to be a secreted protein and may bind Wnt proteins, there is no concrete data presented that would identify any specific properties of human SDF-5 protein or that suggests on any level that SDF-5 is capable of regulating the transcription of any genes. The general speculation in the specification does not enable the claimed invention having the ability to regulate the transcription of one or more genes. The specification specifically teaches that the ability to use the human SDF-5 protein is based on its homology to murine SDF-5 protein. However, since the specification teaches in Example 7 that murine SDF-5 alone does not regulate the transcription of any genes (p. 54, line 17), if one were to extrapolate the teaching of the specification, as suggested, to the human SDF-5 protein, it appears that the claimed limitation would be inoperable. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

11. If Applicant were able to overcome the rejections under 35 USC 112 first paragraph above, Claims 19, 20, 23, 25 , 29 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a human SDF-5 protein comprising SEQ ID NO:2 does not reasonably provide enablement for a truncated human SDF-5 protein as recited in SEQ ID NO:3 or the claims as written. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim.

The claims are drawn to truncated human SDF-5 proteins. The specification teaches that the invention is based in part on the Von Heginje signal peptide prediction algorithm and that the first 17 to 24 amino acids of SDF-5 appear to be involved in signaling for the secretion of the mature peptide and that it is expected that active species may optionally include the signal peptide and will include amino acid sequences beginning with amino acid residues 1, 18, 19, 20, 21, 22, 23, 24 or 25 of SEQ ID NO:2, the active species of SDF-5 are expected to include those comprising amino acids 1, 18, 19, 20, 21, 22, 23, 24 or 25 to 295 of SEQ ID NO:2 (p. 5, lines 24-35). The specification exemplifies the functional affect of mouse SDF-5 gene product on MLBD13MC-clone 14 cells, wherein treatment with murine SDF-5 in combination with BMP-2 decreased hypertrophic cartilage markers and increased markers for cartilage compared to BMP-2 alone, even though there was no effect of murine SDF-5 alone (p. 53, lines 11-26). One cannot extrapolate the teaching of the specification to the scope of the claims because it is not clear, in light of knowledge well known in the art, why the specification hypothesizes that these truncated versions of SEQ ID NO:2 would be active species. Murine SDF-5 has a 95% sequence similarity to human SEQ ID NO:2 (see Shirozu et al, Genomics 27:273-280, 1996, of record). The species used in the *in vitro* assay demonstrated the effects of the murine SDF-5, but cannot be correlated to the effects of human SDF-5 because it is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology. The effects of dissimilarities between proteins on the structures and functions of those proteins cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function

of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. clearly, with up to a 5% dissimilarity and to mouse SDF-5 and up to a 10% dissimilarity with the claimed truncations, the function of the SEQ ID NO:2 polypeptide, or the claimed truncations, could not be predicted

based on sequence similarity with murine SDF-5 (even if the function of murine SDF-5 were known), nor would it be expected to be the same as that of murine SDF-5. Other than hypothesizing that the first 24 amino acid residues of SEQ ID NO:2 may be involved with signaling, there is no teaching in the specification as to what effect truncation would have on the structure and function of the protein. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and

propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with up to a 10% dissimilarity, to murine SDF-5 protein, the function of the SEQ ID NO:2 polypeptide could not be predicted, based on sequence similarity with murine SDF-5 (even if its function were known), nor would it be expected to be the same as that of murine SDF-5.

12. All other objections and rejections recited in Paper No. 12 are withdrawn.

13. No claims allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
March 5, 2002